Clinical practice

Autopsy proven causes of in hospital mortality in acute stroke

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ABSTRACT

To characterize discrepancies between the causes of death as determined by the clinician and autopsy findings in patients admitted with stroke, we retrospectively reviewed all autopsies on patients died with a diagnosis of stroke. Fifty-eight patients with a diagnosis of stroke died after admission to our tertiary medical center in the past ten years were autopsied. Strokes included ischemic strokes, hemorrhagic strokes and subarachnoid hemorrhages. Thirty-five had complete autopsy and twenty-three patients had autopsy limited to brain only examination. We reviewed the autopsy findings and correlated them to the clinical diagnoses that were extracted from the clinical records. We looked particularly for major discrepancies that could have altered treatment strategies. Discrepancies between clinical diagnoses and autopsy findings were classified into major and minor using the Goldman et al. criteria. Only in three instances there were major discrepancies and therapy may have altered medical management in one of these.

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1. Introduction

The rates of autopsies have substantially declined over the past decades. Data from the Unites States National Center for Health Statistics (NCHS) has shown that the autopsy rate of all deaths decreased from 19.3% in 1972 to 8.7% in 2007.[1] Mortality in stroke patients has declined from 34.8% to 19.4% over the past decade.[2] The NCHS data in 2003 demonstrated that autopsies were performed only in 2% of deaths from cerebrovascular disease. Despite advances in diagnostic techniques, some clinically relevant diagnoses remain undetected and revealed only at autopsy. It helps us understand the pathophysiology and provides feedback to the physician, thus providing a basis for improving quality in patient care.[3] If accurately diagnosed, management might have altered prognosis in some patients. Several factors play a crucial role in establishing an accurate clinical diagnosis, some of which include difficulty in obtaining adequate medical history from patients, the rate at which the condition develops and the goals of care.

Since the diagnosis of acute stroke relies on clinical judgment and supported by radiological findings, the degree of accuracy of antemortem diagnosis and cause of death should be higher than other medical conditions. The main objective was to determine the degree of discrepancy between clinical diagnosis, cause of death and autopsy findings in patients with acute stroke.

2. Materials and methods

All patients of age 18 years and above admitted with an acute stroke from January 2003–July 2012 who underwent autopsies following in hospital mortality were identified from the autopsy registry maintained by the Department of Pathology at the University of Arkansas for Medical Sciences. These included patients with ischemic stroke, hemorrhagic stroke and subarachnoid hemorrhage. These included patients who were directly admitted or transferred to our facility for evaluation of acute stroke. Patients with traumatic etiologies were excluded. Autopsies were performed on whole body or limited to brain only based on family consent and organ donation. A retrospective analysis of medical records for demographics, clinical diagnosis, comorbidities, length of stay, duration of mechanical ventilation, hospital complications, imaging findings and postmortem findings was performed. We reviewed the autopsy findings and correlated them to the clinical diagnoses that were extracted from the clinical records to determine the degree of accuracy. Discrepancies between clinical and autopsy diagnoses were classified only among patients who underwent whole body autopsy using Goldman et al. method[4] as depicted in Table 1. This could not be applied to patients on whom autopsies were limited to brain only; however, the cause of death and major errors in autopsies limited to brain were analyzed.

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Table 1
Goldman classification for autopsy discrepancies.

Major
Class I-Missed major diagnosis that may have altered therapy or survival
Class II-Missed major diagnosis that would not have altered therapy or survival
Minor
Class III-Missed minor diagnosis associated with terminal disease but not directly responsible for death and would not have altered therapy or survival
Class IV-Missed minor diagnosis that were not attributable to the primary disease and may have altered therapy or survival.

3. Results

The average rate of autopsy during this time period at our institution was 8.8% with an average autopsy rate of 40% among patients admitted with acute stroke. All patients admitted with acute stroke that underwent autopsy following in hospital mortality were included.

Over the last ten years we identified 58 patients, of which 36 were men and 22 were women. Of these, 93% of patients were managed in the intensive care unit preceding their death. Their mean age was 54 years (range, 22–90 years). The mean length of hospital stay was 7.4 days (range, 1–127 days). The mean length of days on mechanical ventilation was 5.8 (range, 0–110 days). Of 58 patients, 35 were Caucasians, 21 were African American, 1 Asian and 1 Hispanic. Complete autopsies were performed in 35 patients but limited to brain in 23 patients due to family consent or organ donation.

Major admitting diagnosis was acute ischemic stroke in 18 patients, intracerebral hemorrhage (ICH) in 33 patients and subarachnoid hemorrhage in 7 patients (Fig. 1). Among patients with ischemic stroke (Fig. 2) the most common location was posterior circulation strokes in 9 patients, followed by anterior circulation affecting 6 patients and involvement of both anterior and posterior circulations in 3 patients. The most likely etiology based on clinical evaluation was large vessel disease in 12 patients, cardioembolic in 3 patients, septic emboli in 2 patients and vasculitis in one patient. Most common pathology on autopsy was large vessel disease from severe underlying atherosclerosis of intracranial vasculature in 12 patients, with associated thrombosis in four of these. There was evidence of giant cell arteritis in one patient and septic thromboembolism from gram-negative bacilli in one patient. The intracranial vasculature was normal on autopsy in 4 patients.

Among patients with ICH, the most common location was basal ganglia (16 patients), followed by lobar hemorrhages (8 patients), brain stem (6 patients) and cerebellum (3 patients) (Fig.3). The most common mechanism was hypertension causing 26 hemorrhages followed by coagulopathy in 7. Among the hypertensive ICH, cocaine was the triggering factor for the spike in blood pressure in
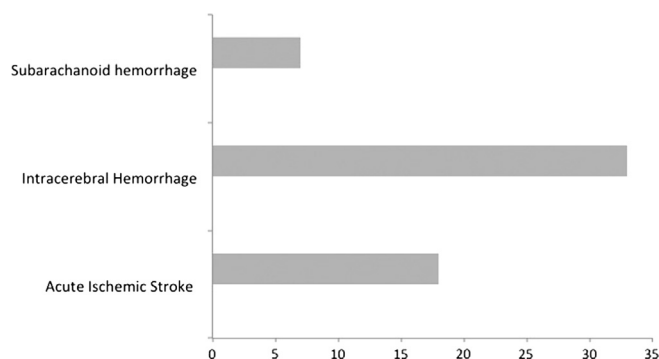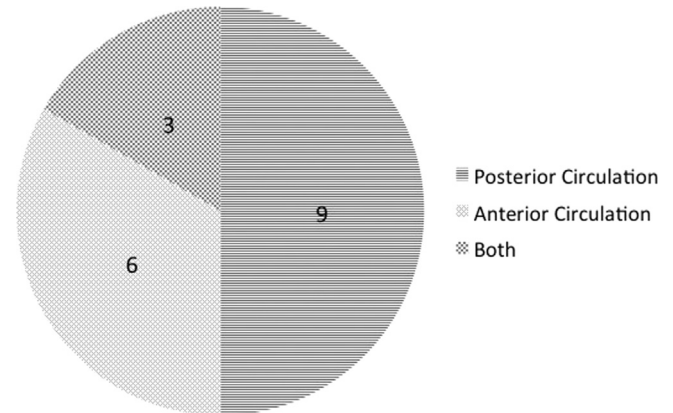
Fig. 2. Location of ischemic stroke.

five patients. There was evidence of moderate atherosclerosis of intracranial vasculature in 17 patients, but normal in the rest. The grade of hemorrhage using the ICH-Grading Scale (Ruiz-Sandoval et al.) was 11 in 24 patients and 12 in 9 patients.

The most common grade in subarachnoid hemorrhage was modified Fischer 4 followed by modified Fischer 3.[5] Among the 7 patients with subarachnoid hemorrhage, there was evidence of moderate atherosclerosis affecting 5 patients and normal in the other two patients.

3.1. Discrepancies in patients with complete autopsies

Major discrepancies were identified in two patients (6%-Class I and II each 3%), and a minor error in 37% of the cases. Complete agreement between clinical and autopsy diagnosis was identified in 57%. The characteristics of patients with major and minor discrepancies are listed in Table 2 and Table 3. The most commonly missed diagnosis was pneumonia. A clinical diagnosis of pneumonia was made in 29% but on autopsy was 49%.

3.2. Errors observed on autopsies limited to brain

One patient (4%) was clinically diagnosed to have hypertensive intracerebral hemorrhage but had pathological evidence of glioblastoma multiforme adjacent to the hemorrhagic foci upon autopsy. In one patient (4%), clinical diagnosis and autopsy limited to brain was insufficient to explain the cause of death.
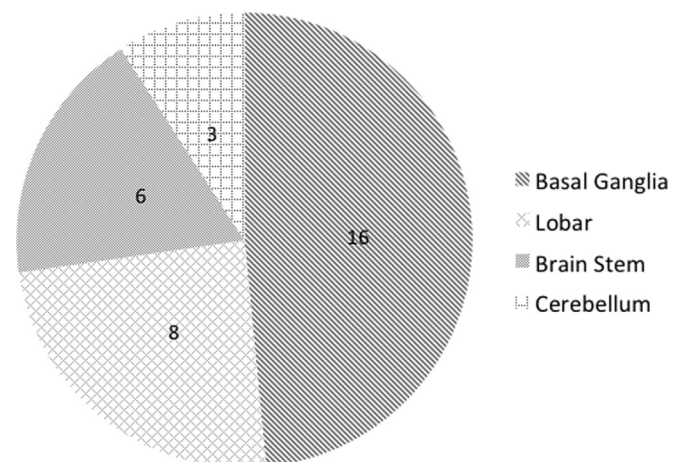
Fig. 1. Major admitting diagnosis.

Fig. 3. Location of hemorrhagic stroke.

3.3. Cause of death (complete and limited brain autopsy)

The major cause of death was related to primary neurological conditions in 88%, followed by medical conditions in 10%. In 2% of our entire cohort, clinical diagnosis and autopsy was insufficient to explain the cause of death.

4. Discussion

The rate of autopsy at our institution during this period was 8.8%, but the rate of autopsy in acute stroke following in hospital mortality was approximately 40%. Although the annual rate of autopsy is low, it is comparable to the national average.

In our retrospective review study, we specifically aimed to determine the major diagnostic discrepancies that could have altered treatment strategies. In the complete autopsy cohort, we identified two major discrepancies from thirty-five autopsies (6% Class I and Class II each 3%) and one error in the limited autopsy cohort, from twenty-three autopsies (4%). Prior studies have reported a major discrepancy rate of 5%–40% among critically ill patients.[6,7]

Our first patient with major discrepancy had invasive aspergillosis that was missed on bronchoalveolar lavage while on amphotericin B, that was diagnosed on autopsy. Although our patient was on an alternative antifungal agent, the first line therapy recommended by the Infectious Disease Society Guidelines of 2008 is voriconazole.[8] A high index of suspicion is required even in critically ill stroke patients. Our second patient was clinically stable after the clipping of intracranial aneurysm and was awaiting discharge to a rehabilitation facility when she developed acute onset of abdominal pain, hypotension that responded to resuscitation with intravenous fluids. In two hours, she became unresponsive and suffered a cardiorespiratory arrest. The cause of her death was discovered only upon autopsy, which revealed a massive retroperitoneal hematoma from 5 cm ruptured iliac artery aneurysm. There was evidence of severe atherosclerotic disease

Table 2
Major errors.

Principle diagnosis	Autopsy diagnosis
Major discrepancies in complete autopsies (Class I and Class II)	
1. 46-year-old immune competent lady with coronary artery disease, congestive heart failure, aortic valve replacement admitted for 18 days with sepsis, coagulopathy, small left frontal intracerebral hemorrhage. Bronchoalveolar lavage revealed *Cryptococcus neoformans* and treated with Amphotericin B	Disseminated aspergillosis
2. 62-year-old hypertensive lady underwent clipping of her ruptured left middle cerebral artery aneurysm was awaiting transfer to a rehabilitation facility. On the 13th day she had acute onset of abdominal pain, hypotension, unresponsiveness requiring resuscitation.	Ruptured right common iliac artery aneurysm
Major errors in autopsies limited to brain	
1. 49-year-old hypertensive male with large left thalamic intracerebral hemorrhage with extension into midbrain and intraventricular hemorrhage, Glasgow coma score −3, blood pressure of 225/113 mm Hg. Failed to improve with external ventricular drain, medical management and removed from intensive care support after 5 days	Glioblastoma multiforme

Table 3
Minor discrepancies.

Autopsy findings	No of patients
Pneumonia	7
Pulmonary embolism	2
Renal cell cancer	2
Infective endocarditis	2
Renal thrombus	1
Deep vein thrombosis	1

affecting her aorta and coronaries, which in addition to hypertension may be the etiology of these two aneurysms. Given the acuteness of her symptoms, even if a premortem diagnosis was made, there may have been insufficient time for its appropriate management. This highlights the value of autopsy in the modern era especially in explaining the cause of unexplained deaths. Our third patient was diagnosed with a hypertensive intracranial hemorrhage but a limited brain autopsy revealed an underlying glioblastoma multifome. The incidence of brain tumor related ICH has been reported in 4.4%–7.2%.[9,10] Major intratumoral hemorrhage has been reported in 1.5%–2.4% of patients with brain tumor. A high index of suspicion is required to diagnose these. The location of his intracranial hemorrhage caused severe brain damage from mass effect and edema resulting in a coma, which failed to respond to medical therapy. Although a premortem diagnosis of this would have been made upon admission, the overall outcome might not have changed due to coma from extensive brain damage and failure to respond to medical therapy.

The rate of minor discrepancy in our cohort was 37%. The minor discrepancies were primarily from medical conditions, pneumonia being the most common. Complete agreement between clinical diagnosis and autopsies were noticed in 57% of patients. The criteria for antemortem diagnosis of pneumonia were presence of chest radiograph infiltrates and 2 of the 3 clinical criteria (leukocytosis, fever, purulent respiratory secretions). Pneumonia complicating acute stroke has been reported from 6.9% to 47%,[11,12] with increased incidence in critically ill patients. In our cohort a clinical diagnosis of pneumonia was made in 29% but was 49% on autopsy, but 93% of our patients were critically ill and managed in the intensive care unit, which explains for such high incidence. Appropriate treatment in these patients would not have changed outcome since they died primarily from neurological conditions. Discrepancies, like missed infections and thromboembolic complications found in our study are similar to those published previously, emphasizing the importance of having a high index of suspicion.[13]

The most common cause of death was related to the primary neurological event followed by medical conditions. All patients who died towards the end of second week and more (except one who had rebleeding at a new site) died from medical conditions. This is similar to a prior study that demonstrated a bimodal distribution in early mortality.[14] The first peak occurred during the first week and the second during the second and third weeks. The majority of deaths during the first week were from transtentorial herniation and towards the end of the second week from relative immobility (pneumonia, pulmonary embolism and sepsis).

In one patient (4%) of the limited autopsy cohort, both clinical diagnosis and limited autopsy was insufficient to explain the cause of death. Hence in situations where the cause of death cannot be explained clinically, a whole body autopsy should be urged.

Some major limitations of our study include a low autopsy rate, small cohort, single center study, retrospective analysis, lack of a control group, a large selection bias that motivate an autopsy request despite offering this to all families and limited brain biopsy and including only patients who died from severe illness. Larger prospective studies are required to confirm these results.

5. Conclusion

Among patients admitted with acute stroke the diagnostic accuracy for major diagnosis and cause of death was high in our cohort.

Ethical approval
None.

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None.

Conflict of interest
None.

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